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EXAMINER	
GAMETT, DANIEL C	
ART UNIT	PAPER NUMBER
1647	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/836,750	ELIA, JAMES P.	
	Examiner	Art Unit	
	DANIEL C. GAMETT	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 June 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *See Continuation Sheet* is/are pending in the application.

4a) Of the above claim(s) *6-235 and 240-242* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *236,238,239,243,244,247,250,251,253,257-263,268-271,280-285 and 288-290* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Continuation of Disposition of Claims: Claims pending in the application are 6-236,238-244,247,250,251,253,257-263,268-271,280-285 and 288-290.

DETAILED ACTION

The Art Unit location of your application in the USPTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Art Unit 1647. The Examiner for this Application is now Daniel C. Gamett.

1. A request for continued examination under 37 CFR 1.114 was filed in this application after appeal to the Board of Patent Appeals and Interferences, but prior to a decision on the appeal. Since this application is eligible for continued examination under 37 CFR 1.114 and the fee set forth in 37 CFR 1.17(e) has been timely paid, the appeal has been withdrawn pursuant to 37 CFR 1.114 and prosecution in this application has been reopened pursuant to 37 CFR 1.114. Applicant's submissions filed on 03/18/2008 and 06/06/2008 have been entered.

2. Claims 1-5, 237, 245, 246, 248, 249, 252, 254-256, 264-267, 272-279, 286, and 287 are canceled. Claims 6-235 and 240-242 remain withdrawn from consideration as being directed to a non-elected invention. Claims 236, 238, 239, 243, 244, 247, 250, 251, 253, 257-263, 268-271, 280-285, and 288-290 are under examination.

3. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior office action.

Claim Rejections - 35 USC § 112

Maintained Rejection

4. Rejection of claims 236, 238, 239, 243, 244, 247, 250, 251, 253, 257-263, 268-271, and 280-285 under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement is maintained and hereby extended to include new claims 288-290. The claim(s)

contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The basis of this rejection is of record. The specific arguments set forth in the Examiner's Answer mailed 01/24/2008 are maintained, but will not be repeated in the instant office action except where clarification may be deemed useful, omissions may be corrected, and to address matters raised in Appellant's Reply Brief filed 03/18/2008.

5. Before addressing each the arguments in Applicant's Reply Brief, it seems appropriate address certain matters of interpretation at the onset. First, on pages 13-14 of the Reply Brief, Applicant asserts that the claims do not stand or fall together, and complains that the Examiner has not considered them separately. All of the claims, including new claims 288-290, require administration of a stem cell harvested from bone marrow (e.g. claims 261-263, 268, 269), or some factor within Applicant's broad genus of growth factors (claims 236,238, 239, 243,244, 247, 250, 251, 253, 257-260, 270,271, 281-285), and growing new cardiac muscle and a new artery. The rejection of record holds that methods comprising these elements that are essential and common to all of the claims are not enabled by the disclosure. If embodiments defined by particular limitations (e.g "a dead portion" (claim 238) or "a damaged portion" (claim 239)) were enabled, a scope of enablement would have been indicated. Therefore, the claims appear to be considered as a group because no recited limitation rescues any claim from lack of enablement.

6. A second matter is the breadth of the claims. Referring to the Examiner's Answer, Applicant argues (Reply Brief, p.20), "the Examiner incorrectly states that "the broadest claims merely recites 'growth factor'." The Examiner apparently has overlooked the fact that a species requirement was made and that Appellant elected cells. Accordingly, the broadest claims under

rejection are cells with the narrowest claims calling for bone marrow stem cells." Thus Applicant argues, erroneously, that Applicant's election of species somehow changes the plain meaning of the words that are still present in the claims. The broadest instant claims (236,238, 239, 247, 250, 251, 257-259, 261-263, 270,271, and 281-285) recite "growth factor", which according to the specification may be any organic and inorganic matter, bacteria, viruses, proteins, derivatives of cellular products, genes, extracellular matrices, living organisms. Claims 243, 244, and 260 recite all cells, cellular products, or derivatives of cellular products. Claim 253 recites any gene and any cell. These claims recite non-elected subject matter and, if allowed, they would encompass the entire recited scope regardless of Applicant's species election. It is appropriate and necessary that the entire recited scope should be considered with regard to enablement. While the claims are being discussed primarily with respect to the narrowest embodiments (administration of a stem cell harvested from bone marrow), it must be understood that even if the narrowest claims were enabled (which they are not), such enablement would not extend to the methods that comprise placing any or all of the genus of "growth factors" or all cells, cellular products, or derivatives of cellular products.

7. In this regard, Applicant (Reply Brief, p.21) takes issue with the Examiner's Answer at page 29, wherein the Examiner states that sources of energy are growth factors, relying upon pages 20 and 21 of the specification. Applicant points out that a reading of these pages leads one to the conclusion the Appellant did not define energy within the disclosed class of growth factors. It is agreed that sources of energy are merely described as means to activate growth factors, not as growth factors *per se* (p.20, line 30 to p,21, line 3). This distinction makes little difference to the size of the asserted genus of growth factors and does not alter the discussion of

the scope of "growth factor" as it is used in the claims. This does raise an interesting question, though. If sound, electricity, and heat, which are mentioned in the midst of a discussion of "growth factors", are not "growth factors", then how is it that bone marrow stem cells, which are never explicitly identified as "growth factors" anywhere in the specification, are "growth factors" as recited in the claims? The relationship of "cells" to "growth factors" will be further discussed herein with respect to the clarity (or lack thereof) with which the instant specification teaches the claimed methods.

8. A major issue raised in Appellant's Reply Brief filed 03/18/2008 concerns post-filing date publications. "Enablement, or utility, is determined as of the application filing date." *In re Brana*, 51 F.3d 1560, 1567 n.19, 34 USPQ2d 1436, 1441 n.19 (Fed. Cir. 1995). It is noted that Applicant "agrees that the state of the art *at the time the instant application was filed* does not disclose the growth of new arteries (Reply Brief, p.5, emphasis added). Therefore, even if the post-filing references provide evidence of cardiac muscle and artery formation, the remaining controversy is whether the post-filing results "confirm Appellant's disclosed and claimed results, i.e., heart repair and formation of a new artery" as asserted by Applicant, or they constitute evidence of the further act of invention that was required before achieving any repair of dead/damaged heart tissue (Examiner's Answer, p.7, p.23, p.36).

9. On page 4 of the Reply, applicant states, "At page 8, paragraph 4 of the Answer, the Examiner raises a new issue regarding timing of treatment by citing Murry et al. (hereinafter "Murry"). Apparently, the Examiner relies upon Murry, for the first time in this record, to bolster the prior allegation that timing of treatment required a great amount of experiment." Applicant

then suggests that the Examiner disregarded three Strauer et al. publications of record in citing Murry. This mischaracterizes the cited section of the Examiner's Answer. The cited paragraph was not about the amount of experimentation, but rather about the complexity of the invention. The quotation from Murry addresses the timing of treatment, but this was only used to provide an example of complexity, not to "support Examiner's position regarding timing of treatment" as asserted in Applicant's argument. Therefore, the use of the Murry reference of record is entirely appropriate in the context. In fact, the Examiner's Answer is not "the first time in the record" in which the Murry reference was cited to indicate the complexity of the invention—Murry was cited in precisely the same way in the office action mailed 09/22/2006, page 13, second paragraph. The Strauer references were not disregarded, as Strauer was in fact the first reference cited in the paragraph of the Examiner's Answer. Applicant's assertion that the Strauer references are more probative of the timeliness issue is irrelevant because the subject at hand was not the issue of timing.

10. Applicant argues that Applicant has "never relied upon any extraneous post-filing date publications to support enablement", but rather asserts that post-filing date publications "confirm Appellant's disclosed and claimed results, i.e., heart repair and formation of a new artery". Applicant then (pp.6-8) discusses Orlic, Dohmann, and Strauer 2002 references of record, to the effect that these references disclose formation of new arteries. Applicant cites experimental results in Orlic that show evidence of new endothelial cells and new smooth muscle cells in the hearts of rats that had received bone marrow cells. Applicant quotes Strauer as teaching that bone marrow hemangioblasts contribute to the formation of new vessels and that bone marrow hematopoietic cells differentiate into cardiomyocytes, endothelium, and smooth muscle.

Applicant points to immunochemistry findings in Dohmann that show evidence of arterial walls and smooth muscle cells. Applicant points out that Dohmann used the word "new" to describe the formation of vessels.

11. The rejection of record holds that the post-filing references of record do not teach new artery formation, at least in the sense that the term "new" is used in the instant claims and specification. In this regard, Applicant asserts (Reply, p.11) that on pages 14-16 of the Examiner's Answer "inaccurately cites descriptive language from three portions of the specification". The charge of inaccuracy is difficult to understand, given that the cited portions were copied verbatim from the specification. Applicant takes issue with the use of the term "de novo" in the rejection of record. Applicant first indicates that the term "de novo" is not used in the specification and then argues that "Appellant has consistently used the term "new" to describe formation of a cardiac muscle and an artery or portion of an artery that was not in existence before the injection of the stem cells." Applicant thus presents a semantic argument, which does nothing to refute the point made in the Examiner's Answer and in the rejection of record. What else does "de novo artery formation" mean, if not "formation of an artery that was not in existence before the injection of the stem cells"? It is clear from Applicant's argument that the full scope of the term "new" as it is used in the instant claims includes formation of cardiac muscle and an artery that were not in existence before the injection of the stem cells. The Examiner's Answer (pp.14-16) pointed out that the cited sections from the specification at p. 54 and p. 56 clearly show that the specification contemplates entirely new arteries. The section on p. 54 clearly makes a distinction between new arteries and new sections of arteries. The instant claims recite "forming a new artery", not "forming a new section of an artery". Therefore, the

claims are drawn to methods of causing formation of an artery that did not previously exist, regardless of whether one chooses to refer to such formation as "de novo artery formation" or "forming a new artery". The claims have been properly construed according to the specification and according to Applicant's own characterization of the meaning of "new", and it is altogether proper that they should be rejected on the basis of an analysis of whether the specification provides enabling support for methods of causing formation of cardiac muscle and an artery that did not previously exist. Therefore, Applicant's arguments regarding use of the term 'de novo', which are reiterated throughout the Reply Brief, are not persuasive as to the merits of the rejection of record. As demonstrated in the Examiner's answer (paragraph bridging pages 16-17), the post-filing references indicate that stem cells can be administered without any evidence of new artery formation. The fact that certain researchers were *not trying* to form an artery, as Applicant argues (Reply Brief, p. 15 and p. 22) is irrelevant. Artery formation does not necessarily follow after administration of any kind of growth factor, any cell, or bone marrow stem cell at any selected site, which would be required for the instantly claimed methods. Again, the issue is that the instant specification does not teach the skilled artisan *how* to manipulate these allegedly old materials and methods to achieve the remarkable effects required by the claims (growth of a new artery, repair of dead/damaged heart tissue).

12. Applicant argues (pp.12-13) that the term "new" and been introduced into the claims in response to a previous suggestion from an examiner during an interview that this would distinguish the claims over prior art (Murry). It remains true that recitation *in the claims* of formation of an artery that did not previously exist (i.e. a new artery) distinguishes the present claims over Murry. The question at hand however, is whether the specification provides enabling

support for methods of causing formation of a new artery. Applicant indicates "*Appellant's counsel* stated that the claims would be amended to include the words "forming new arteries" rather than "forming arteries" and further pointed out that the specification supported such amendment" (emphasis added). Nothing in the record indicates that any examiner agreed that the new limitation "forming new arteries" was enabled by the instant specification. Once "forming a new artery" was introduced into the claims, the claims were examined accordingly, with the meaning of the term interpreted as indicated in the specification.

13. Applicant addresses (Reply, p. 15) the Nabel reference of record. Applicant had previously cited Nabel as teaching an angioplasty balloon catheter and providing guidance regarding back flow prevention and contact time, from which Applicant had argued that Strauer et al. 2002 did not have to perform any experimentation to achieve successful heart repair by administering stem cells. The Examiners Answer, at page 18, pointed out that nowhere do Strauer et al. refer to Nabel et al. even though numerous other post-filing date publications are cited by Strauer et al. 2002 at pp. 1916-1918. Furthermore, nowhere do Nabel et al. report the type of experimental detail provided by Strauer et al. 2002 or growth of a new artery or repair of dead/damaged heart tissue. Nabel did, however, did disclose placement of cells at a selected area of a patient with ischemic heart, which inherently comprises a dead/damaged portion (see abstract and col. 2, li.40-50). Thus, Nabel performed a procedure that operationally meets all of the limitations of all but the narrowest of the instant claims, but did not observe the same effects. It follows that, considering the differences between Nabel et al. and Strauer et al. 2002, it is clear that Strauer et al. 2002 provide the information as to *how* to achieve repair of heart tissue by

administration of cells, whereas Nabel et al. (and the instant specification) do not. Now, Applicant argues (Reply, p.15) that, "A reading of Nabel clearly shows that there was no objective or attempt made to form a new artery and repair dead or damaged portions of a heart, and thus *Nabel is not relevant to the enablement of the claimed invention*" (emphasis added). Thus, Applicant presents contradictory arguments that the Nabel reference provides "off-the-shelf" materials and methods so that the instantly claimed results (or those of Strauer, 2002) could be achieved with minimal experimentation, and yet the Nabel reference is irrelevant to enablement of the instant claims. It remains clear, therefore, that simply being aware of angioplasty balloon catheters, as taught by Nabel, does not mean that heart repair by administration of bone marrow stem cells can be achieved without experimentation. The work performed Strauer and others constitutes evidence of the further act of invention that was required before achieving any repair of dead/damaged heart tissue.

14. Applicant further argues that "Nabel does not disclose using the type of cells called for by the present invention, i.e., pluripotent stem cells of the type contained in bone marrow, and therefore cannot relate to the enablement of treating a dead or damaged portion of a heart by growing new arteries and cardiac muscle." Applicant is reminded that only instant claims 261-263, 268,269, and 288-290 recite bone marrow stem cells. The cells disclosed in Nabel meet the limitation of all other instant claims if Applicant's definition that includes "cells" within the genus of "growth factors" is applied. Further, as noted above, Nabel performed a procedure that operationally meets all of the limitations of all but the narrowest of the instant claims, but did not observe the same effects. Thus, Applicant has not persuasively argued against the finding that simply knowing how to inject cells into a heart is not enough information to successfully

perform a method of heart repair by administering stem cells. Again, work performed Strauer and others constitutes evidence of the further act of invention that was required before achieving any repair of dead/damaged heart tissue.

15. It has been pointed out that Strauer et al. 2002 state clearly and in detail that cell population is critical at pp. 1916-1917 (Examiner's Answer, p 21). This determination of a critical cell population has been held to be an example of the experimentation that would be required before achieving any repair of dead/damaged heart tissue. In response, Applicant has argued that Strauer did not describe any experimental protocol to determine the appropriate cell population (Reply Brief, p. 15). In the Reply Brief, Applicant argues that "it is clear from Strauer 2002 that, at the pages referred to by the Examiner, Strauer 2002 appears to have relied upon the prior work of others, including the selection of cell population, rather than upon experimentation." This is not persuasive, first, because it is still clear that considerable experimentation was done, if not by Strauer then by others, in order to determine the effective cell population. Secondly, it has been pointed out that "In peer-reviewed journal articles, failed experiments are generally not reported, and thus when the successful regimen is disclosed, it cannot be concluded that no experimentation was done" (Answer, p.20). In response, Applicant (Reply Brief, p. 18) argues that, "the Examiner, for the first time, improperly imputes that Strauer 2002 may have conducted, but not reported, failed experiments in an effort to bolster her case. The Examiner fails to provide evidence that such conduct is commonplace in the medical field, and for good reason. Such rank speculation does not rise to the level of objective evidence." The Examiner's position is supported, for example, by Goetz, Wired Magazine 15.10; September 25, 2007). Goetz discusses "dark data", which includes negative results, unexplained

results that are the opposite of expected, and "failures" that generally are not revealed for various reasons. Goetz further references the *Journal of Negative Results in Biomedicine*, a journal launched in 2002, and Nature Precedings, a Web-based forum, which have attempted to address the fact that "dark data" may in fact be useful to other researchers. Goetz further laments that these efforts are the exception rather than the norm. The lack of disclosure of negative results is a persistent problem as evidenced by a December 12, 2007 post to the Biotech Bits blog at Nature.com, which proposed an online repository of "bad protocols"; the responses to the proposal were universally positive. Delamont and Atkinson (2001, Social Studies of Science 31: 87-107) point out that researchers in training learn to remove mention of indeterminate aspects from public accounts of their research, one reason being that these are associated with failures that occur prior to the acquisition of skills (see Abstract). To this documented evidence, the present examiner, having spent several years engaged in basic research as a primary occupation, adds official notice that the statement "In peer-reviewed journal articles, failed experiments are generally not reported, and thus when the successful regimen is disclosed, it cannot be concluded that no experimentation was done" is an accurate assessment. Thus, the previous examiner's statement regarding undisclosed experimentation is "rank speculation" only to those unfamiliar with the process of basic research. Therefore, Applicant's arguments do not refute the points made in the rejection of record with respect to the lack of guidance in the instant specification and the amount of experimentation that would be required to perform the claimed methods. Regarding Strauer et al. 2002, the examiner maintains that this publication constitutes evidence of the further act of invention that was required before achieving any repair of dead/damaged heart tissue. *Any amount of experimentation*, such as the various determinations performed by

Strauer, regarding what cell population to use, what delivery method to use, and when cells should be transplanted, would be *infinitely more than is presented in the instant specification* in support of the claimed methods.

16. Applicant has asserted to have "never relied upon any extraneous post-filing date publications to support enablement" and to have "consistently relied upon the specification of the instant patent application" (Reply Brief p.9). It is, therefore, proper that this office action should focus on the specification as filed. This will bring the significance of the post-filing date publications into perspective. The post-filing references under discussion deal with methods comprising administration of cells. Although these references indicate that administered cells contribute to the formation of new vessels that comprise endothelial cells and smooth muscle cells, they do not "confirm" the teachings of the instant specification, as asserted by Applicant (p.5, p.21). On the basis of the instant specification, Applicant cannot take credit for predicting the results achieved by others. As previously noted (Office Action 02/16/2006, page 8), it is improper to pick and choose among unconnected sections of a specification in an attempt to capture another research group's post-filing date discoveries. The most favorable characterization of the teachings of the instant specification is that by circuitous logic not explicitly presented in the disclosure, one of skill might surmise that a method to use stem cells to grow an artery was suggested. The concept of using any kind of cell to grow an artery relies on selection of portions of the specification that contain the desired words, interpreting them in a manner that is contrary to the ordinary meanings of the key terms in the art, and putting them together, without specific prompting in the specification.

17. For example, although the cited sections from pages 54, 56, and 62 (Examiner's Answer pp.14-15) are useful in determining what is meant by "new" artery, they do not teach or guide the administration of stem cells for the purpose of growing and artery or repairing a damaged heart. The cited sections are taken from Examples 18, 19, and 36, which are directed to administration of VEGF165 cDNA. These examples do not even suggest the use of bone marrow stem cells, any kind of stem cell, or cells of any kind, to grow and artery or repair a heart, much less provide guidance for the use of bone marrow stem cells for these purposes. As indicated in the Examiner's Answer (p. 20), any example, real or prophetic, involving administration of nucleic acids provides no guidance regarding administration of cells, because the scientific considerations of handling, dosage, carriers, etc. are completely different. Much of Applicant's Reply Brief concerns the adequacy of Examples 18, 19, and 36 in teaching a method of using bone marrow stem cells to grow and artery and repair a heart.

18. On page 17 of the Reply, Applicant states, "At pages 20, 33, and 34 of Answer, the Examiner first alleged that the selection of dosages for cells and genes involves completely different scientific considerations. Again, the Examiner offered no reasoning or evidence in support of such allegation." This is akin to saying, "Your analogy of comparing apples to oranges is not convincing because you have not provided evidence that apples and oranges are different". It is remarkable that any question of whether cells and genes are different from one another would even come up in a serious discussion of a state-of-the-art biotechnological invention. For evidence that the scientific considerations regarding methods comprising administration of cells as opposed to cDNA are completely different, one need look no further than the US Patent classification system. Methods of *in vivo* treatments involving whole live

cells as opposed to nucleic acids are separately classified: class 424 subclass 93.1 (cells); class 514, subclass 44 (polynucleotides). These separate classifications indicate a different status in the art such that it is well known that cell therapy and gene therapy are not obvious variants of one another.

19. This does not mean that it is not possible to claim and perform a method in which cells, cDNA, and/or polypeptide growth factors are used together, as in U.S. Patent No. 5,980,887 granted to Isner et al, (Isner '887), dependent claims 2 and 3, for example. Applicant (Reply Brief, p. 16) points to the Isner '887 patent, and argues that while said patent teaches administration of both genes and cells to a human patient to grow an endothelial tissue layer, it does not indicate that materially different protocols are required for genes and cells. This is not persuasive for the following reasons. Isner '887 taught and claimed a method for inducing the formation of new blood vessels comprising administration of isolated endothelial progenitor cells (see claim 1), and claimed further embodiments of the method wherein cells and polypeptide growth factors or nucleic acids encoding growth factors, are used together to complement one another to achieve growth of new blood vessels (see claims 2 and 3, for example). While Isner described extensively the preparation, handling, and dosing of the cells, nowhere does Isner imply that the methods described for cells could or should be applied to nucleic acids or polypeptides. The intrinsic differences among cells, polypeptides, and nucleic acids are generally understood by persons of skill in the art, so there would be no reason for Isner to explicitly state that the methods of their handling, dosage, carriers, etc. are materially different. Applicant is not arguing that cells and various molecules can be used to complement one another to achieve an end, as taught in Isner. Applicant's argument that Examples 18, 19, and 36 teach and guide the

use of stem cells to grow an artery relies on the notion that a teaching of VEGF cDNA for growing an artery (Examples 18, 19, and 36) first causes one of skill in the art to envision using stem cells for the same purpose, and then provides guidance for how to do it. The allowed claims in the '887 patent do not indicate that each of the recited components are interchangeable. If a teaching of "cells" inherently encompasses cDNA and protein factors, then why bother with dependent claims that recite these *further* components? If recitation of cDNA encompasses cells, why is claim 1 separate from the others? The Isner '887 patent does not support the assertion that the USPTO has ruled that one of skill in the art would read a teaching about genes or protein growth factors and thereby gain guidance for the use of stem cells for the same purpose.

20. Applicant's argument that Examples 18, 19, and 36, which teach administration of nucleic acids, teach and guide the use of stem cells, relies on the notion that stem cells and VEGF cDNAs are both species of "growth factor", as defined by Applicant, and that "One reasonably skilled in the art appraised of such disclosure would readily be able to predict and comprehend that stem cell growth factors are equivalent to cDNA clones in providing the desired artery formation" (Appeal Brief, p.26). "It is clear that Appellant's specification treated genes and cells as belonging to a class of compositions for promoting soft tissue growth" (Reply Brief, p. 16-17). In this regard, it is important to note that the concept of "cell as a species of growth factor" does not exist in the art. First, consider the following dictionary definitions of "growth factors":

From the Online Medical Dictionary:

> **growth factors**
>
> Proteins involved in cell differentiation and growth. Growth factors are essential to the normal cell cycle, and are thus vital elements in the life of animals from

conception to death. Among other things, they mediate foetal development, play a role in maintenance and repair of tissues, stimulate production of blood cells, and, gone awry, participate in cancerous processes.

From the Dictionary of Cancer Terms:

growth factor

A substance made by the body that functions to regulate cell division and cell survival. Some growth factors are also produced in the laboratory and used in biological therapy.

From the Life Science Dictionary:

2. **growth factor**
Author: Susan A.Hagedorn
Definition: A serum protein that stimulates cell division when it binds to its cell-surface receptor.

Alberts *et al.*, in Molecular Biology of the Cell, 4th Ed, 2002, write in Chapter 17:

The factors that promote organ or organism growth can be operationally divided into three major classes:

1. *Mitogens,* which stimulate cell division, primarily by relieving intracellular negative controls that otherwise block progress through the cell cycle.

2. *Growth factors,* which stimulate cell growth (an increase in cell mass) by promoting the synthesis of proteins and other macromolecules and by inhibiting their degradation.

3. *Survival factors,* which promote cell survival by suppressing apoptosis. Some extracellular signal molecules promote all of these processes, while others promote one or two of them. Indeed, the term *growth factor* is often used inappropriately to describe a factor that has any of these activities. Even worse, the term *cell growth* is often used to mean an increase in cell number, or *cell proliferation.*

21. Although Alberts *et al.*, call for a precise definition that is slightly at odds with the dictionary definitions cited above, all sources agree that a "growth factor" is "a factor that acts upon cells" not "a factor which *is* a cell", as Applicant wishes for it to mean.

22. An EAST search covering the worldwide patent literature yielded 418 documents wherein the expression "cellular growth factor" as not part of the expression "cellular growth factor receptors". This criterion was chosen because the expression "cellular growth factor receptors", of course, refers to receptor molecules on cells. The "key word in context" results for all 418 documents will be entered into the record as Examiner's search notes. The results will, therefore, be available to Applicant through PAIR. In all 418 documents the Examiner found not a single instance where "cellular growth factor" could be logically construed to mean "a growth factor which is a cell" as Applicant wishes for it to mean. In the few instances where the key word in context leaves room for doubt, the associated full specification always confirms that the term "cellular growth factor" always means "a factor that acts upon cells". With regard to non-patent literature, a search of Medical Subject Headings database maintained by the National Library of Medicine (www.nlm.nih.gov/mesh/2007/MBrowser.html), using "growth factor" as the query term, yields a 24-page list of factors (see search notes). Not one cell is listed. Therefore, expressions such as "growth factors, including cells, such as stem cells" or "cellular growth factors such as stem cells" are outside of the ordinary usage of these terms, regardless of the academic degree held by the person using them.

23. In view of the foregoing medical dictionary definitions, textbook definition, and literature searches, Applicant's expectation that one of skill in the art would view "stem cells" and "VEGF cDNA" as species within a larger genus of "growth factors" is totally unfounded. There simply is

no rational scientific basis for one of skill in the art to read "VEGF cDNA" and think "stem cell", without being specifically prompted to do so. The instant specification does not provide that prompting.

24. Further regarding the value of Examples 18, 19, and 36 in guiding the use of stem cells in the claimed methods, Applicant (Reply Brief, pp. 15-16) addresses the question of calculating a dose of cells to use. Applicant's Appeal Brief filed 10/24/2007 contains the following, on page 24: " Appellant's specification describes new artery growth and heart repair by direct injection of growth factor cells in dosage ranging from approximately 6.25×10^6 (Example 18 & 36) to approximately 12.5×10^6 (Example 19)." To say that this is misleading would be an understatement—it is simply not true. The 6.25×10^6 and 12.5×10^6 cell numbers do not appear in the specification. A method for deriving these cell numbers is not in the specification. Examples 18, 19, and 36 do not mention cells of any kind, and so they cannot suggest to the skilled artisan that one should even try to calculate a number of stem cells. A specific method for calculating cell numbers by extrapolation from the amount of plasmid DNA described in the specification was first entered into the record in this case in arguments of counsel. Thus, to arrive at the 6.25×10^6 and 12.5×10^6 cell numbers, one of skill in the art would first need to read Example 18 and perceive a suggestion to use stem cells, even though Examples 18, 19, and 36 do not even mention cells of any kind, and then derive the following method of converting the amount of plasmid DNA to a number of cells to use:

> The conversion for dosages of nucleic acids to corresponding dosages of cells was conducted as follows. Examples 19 and 36 specified dosages of 500 micrograms (μg) and 250 μg, respectively. The weight of nucleic acids of an average cell was considered to equal 40 picograms (pg). The described dosages of 250 and 500 μg when converted to pg by multiplying by 10^6 equals 250×10^6 pg and 500×10^6 pg. Since nucleic acids of an average cell have an average weight of 40 pg, a conversion is made by dividing 250×10^6

and 500 x 10^6 by 40 to arrive at the equivalent cell dosages, which are 6.25 x 106 and 12.5 x10^6, respectively.

25. For Applicant to say that the specification even suggests direct injection of cells in dosage ranging from 6.25 x 10^6 to 12.5 x 10^6, the above extrapolation method would need to be so commonly used and widely known that one of skill in the art would perceive it to be implicitly present in the specification. If, as Applicant contends, the use of the amount of recombinant plasmid DNA in a gene therapy protocol to calculate the number of cells to use in a cell therapy procedure is well known in the art, then numerous examples of extrapolations like the one in question should easily be found in the peer-reviewed scientific literature or the patent literature. Such examples would show that this method of extrapolation was well known in the art, so that its absence from the specification would be justified. The matter would be settled if such examples were entered into the record. Applicant has not provided any such example.

26. It is noteworthy that the Isner '887 patent cites inventor Isner's earlier work using a VEGF plasmid to indicate feasibility of gene therapy for modulating angiogenesis (col. 2, lines 19-23). If amounts of plasmid DNA were routinely usable as a guide to the number of cells to use, one would think the inventor Isner, an acknowledged expert in both gene therapy and cell therapy, would have mentioned it, but nowhere does the '887 patent suggest that the amount of plasmid DNA was used as a guide for the amount of cells to use in the pioneering cell therapy disclosed in the patent. Isner, in fact, discusses shortcomings of plasmid-based gene therapy, pointing to a need for means to more precisely regulate angiogenesis at a given location (col. 2, lines 24-35). It is clear from the '887 patent that inventor Isner viewed gene therapy and cell therapy as distinct methods, each with its own advantages, disadvantages, and technical features.

If inventor Isner did not see guidance for cell therapy in his own work with gene therapy, why would any person of skill in the art draw the opposite conclusion by reading the gene therapy examples in the instant specification?

27. Applicant has characterized the method as "a straightforward weight conversion for estimating dosages of cells from weights of nucleic acids that has been successfully practiced by medical professionals over some fifty years of cell therapy procedures." In response to criticism of this conversion method (Examiner's Answer pp.33-34), Applicant has entered, with the Reply Brief, Declarations by Dr. Richard Heuser (Exhibit C) and Dr. Andrew E. Lorincz (Exhibit D), each of which cites another Exhibit D which includes the conversion copied above, and conversion tables contained in Exhibit E. As the independent declarations of Drs. Lorincz and Heuser are identical *verbatim*, they will be responded to jointly.

28. Drs. Lorincz and Heuser state that studies involving conversion of the average content of nucleic acids per cell in human marrow cell have been routinely conducted and accepted by skilled scientists for over 50 years. Drs. Lorincz and Heuser supplied excerpts from three publications illustrating such conversion. Drs. Lorincz and Heuser further state that DNA content is substantially consistent from tissues of any given species. None of these facts are disputed. None of these facts speak to the issue at hand. Example 18 describes the administration of a *plasmid DNA vector comprising VEGF cDNA*. The conversion under discussion purports to calculate a number of cells based an amount of *plasmid* DNA. The term plasmid was coined in 1952 (Plasmids; Histories of a Concept, http://histmicro.yale.edu/mainfram.htm). Techniques for making cDNA (copy DNA made by reverse transcription of mRNA), and for using plasmid vectors propagate and express cDNA in cells were developed in the 1970s. Scientists 50 years

prior to the filing date of the instant specification (1998) would not recognize the terminology or even imagine the concept of the conversion described in Exhibit D. Therefore it is impossible that Applicant's assertion that the described method has been practiced by medical professionals over some fifty years to be true. Drs. Lorincz and Heuser conclude that the conversion depicted in Exhibit D is *consistent* with the extrapolations that have been performed for over 50 years (emphasis added). This carefully worded conclusion is not challenged, but it is clear that the consistency extends only to the point that the extrapolations involve math and DNA; any further comparisons would be impossible. Furthermore, the question is not whether a skilled artisan would *know how* to perform the calculation as Applicant, citing the paragraph 6 of declarations, suggests on page 19 of the Reply Brief. The math is simple. The relevant question is: in the event that a skilled artisan, upon reading an example that does not mention cells of any kind, perceived a need to calculate a number of cells, would the artisan arrive at this method without having been specifically instructed?

29. Isner et al., (*Circulation.* 1995; 91:2687-2692) describe construction of the plasmid phVEGF$_{165}$, which appears (without attribution) to be the model for the plasmids mentioned in the specification. According to Isner *et al*. phVEGF$_{165}$ consists of a total of 5651 bp (base pairs). Of these, 3,162 bp are from pUC118, 763 bp are the CMV promoter/enhancer, and 1726 bp are VEGF cDNA. Therefore, the plasmid has one copy of VEGF coding sequences per approximately 5.7 kb (kilobase pairs). According to the data supplied by Drs. Lorincz and Heuser, in the table labeled "II. Some useful nucleotide dimensions", humans have 3 x 10^9 base pairs per haploid genome. This converts to 3 x 10^6 kb. Assuming 1 VEGF gene per haploid genome, 3 x 10^6 kb of human genomic DNA contains the same number of VEGF genes as 5.7 kb

of the plasmid phVEGF$_{165}$. Therefore, the amount of VEGF coding sequence in an equal mass of human genomic DNA and VEGF plasmid DNA differs by a factor of 5.26 x10^5. Inclusion of placental growth factor (PlGF), VEGF-B, -C, and –D as "VEGF genes" in genomic DNA would reduce this factor to about 1 x 10^5. Therefore, it is fundamentally illogical to equate recombinant plasmid DNA to cellular DNA on the basis of mass.

30. As noted by Applicant, these declarations by Drs. Lorincz and Heuser were originally filed in Appellant's co-pending patent application Serial No. 10/179,589. The declarations were submitted in response to an earlier rejection in that case, which contained the following: "Every molecule of the postulated plasmid DNA comprises a copy of the VEGF cDNA. In contrast, VEGF coding sequences would comprise but one of 30-40 thousand genes in genomic DNA (at the time of filing, it was widely believed that the human genome comprised 100,000 genes). Therefore, one of skill in the art at the time of filing would not expect plasmid DNA and genomic DNA to be comparable on a per weight basis." Of course, one of skill in the art of molecular biology would understand that these two sentences embody the same concept of the preceding paragraph herein, albeit with less detail. Drs. Lorincz and Heuser "read and understood" these sentences but did not comment on them. While it is tempting to speculate that the Declarant's silence could be attributed to the fact that molecular biology is not their specialty, it rather seems more likely that Drs. Lorincz and Heuser were carefully refraining from attempting to refute an argument they know to be correct.

31. Furthermore, the difference in gene dosage is just one reason why a person of skill in the art would never attempt such an extrapolation. As in the present case, the rejection in application Serial No. 10/179,589, to which the Declarants were responding, also pointed out that delivery of

genes to a target as recombinant DNA is a technically different process as compared to delivery of native genes within a living cell. No person of skill in the art would deny this. A few of the differences that come readily to mind are, for example, that with DNA one is concerned with chemical stability, efficiency of uptake, stable retention, and subsequent expression of the injected molecule into target cells, whereas with cells separate issues of formation of effective attachment to ECM and neighboring cells, short- and long-term viability, and responses to environmental cues arise. The expression of the recombinant cDNA would be under control of the limited number of enhancer and promoter elements in the plasmid, as opposed the native control elements with the genome. Therefore, even equivalent gene doses would not be expected to yield equivalent amounts of gene product with a plasmid as opposed to a cell. Furthermore, the rejection pointed out that, unlike phVEGF$_{165}$, a cell is not a single molecule designed for expression of a single gene. Every cell expresses thousands of genes and cells possess characteristics and abilities that cannot be accounted for by the presence or absence of a single gene product. As noted (Examiner's Answer p.34), cells are not merely bags of DNA. All of these reasons had been presented to Applicant as to why one of skill in the art at the time of filing would not expect plasmid DNA and genomic DNA to be comparable on a per weight basis prior to the preparation of the Lorincz and Heuser declarations. The Declarants did not address these issues.

32. Furthermore, one of skill in the art would understand that the factors that influence the efficacy of administration of DNA vs. cells can work in opposite ways (*i.e.* tending to require a higher input or permitting a lower input) and the net result cannot be predicted with mathematical precision. Applicant's formula certainly does not rise to the level of a

mathematical model that takes all of these factors into account. Therefore, contrary to Applicant's assertion, the objective evidence indicates that is indeed mere happenstance that the result of the extrapolation overlaps with the number of cells used by Strauer et al. (2002) (Reply Brief, p.19). Finally, even if Applicant had stumbled upon a simple method for determining cell numbers to use in therapy, this would not support any argument for enablement of the instant claims. Such a method would be new to the art and the skilled artisan would not be aware of it unless the specification specifically taught it. The specification does not teach this method, and the method is not implicit in the teachings of the specification.

33. Therefore, returning to the question of whether, in the event that a skilled artisan, upon reading an example that does not mention cells of any kind, perceived a need to calculate a number of cells, would the artisan arrive at Applicant's proposed method without having been specifically instructed, the answer is a resounding, no. The previous Examiner characterized this method as "simply nonsensical and scientifically unsound", which can only be faulted for being too kind.

34. Further with regard to the enablement provided by the instant specification as filed, the Examiner's Answer (p. 12) included the following:

> "Appellant characterizes the inventor's contribution to the medical arts as the combination of using the old materials and techniques to achieve a new result. This has been fully considered but is not found to be persuasive. The issue is that the instant specification does not teach the skilled artisan *how* to manipulate these allegedly old materials and methods to achieve remarkable effects. The instant specification does not exemplify nor provide detailed guidance as to *how* a single organ, part of an organ, tissue, artery, or even a bud can be formed by merely placing cells in a body. Appellant claims to have achieved something no one else had done simply by writing it down. To say that non-obvious and remarkable results can be achieved without doing a single experiment is

> incredible. It is a remarkable achievement to grow a new artery by implanting cells, but Appellant did not do it and Appellant's disclosure does not teach anyone how to do it."

35. In response, Applicant (Reply Brief, p. 10) writes, *inter alia*, "See MPEP 2164.02 and cited case law that stands for the proposition "the mere fact that something has not previously been done clearly is not, in itself, a sufficient basis for rejecting all applications purporting to disclose how to do it." In re Chilowsky, 29 F. 2d 457, 461, 108 USPQ 321,325 (CCPA 1956). Nor does the use of prophetic examples automatically render a specification non-enabled." The record shows that the instant claims are not being "automatically rejected" because of the use of prophetic examples nor because they claim something that has not been done before. It is true that these factors (state of the art, amount of direction or guidance in the specification), taken inconsideration with the other Wands factors, contribute significantly to the finding of a lack of enablement for the instant claims in this case.

36. Applicant further argues (p. 10-11), "Furthermore, the Examiner's requirement for experimentation appears to be in contrast with current Patent and Trademark Office (hereinafter "PTO") practice. In rebuttal to this new issue, Appellant points to recently issued U. S. Patent No. 7,097,832 granted to Kornowski et al, (attached hereto as Exhibit A). Said patent contains claims drawn to a cell therapy treatment of humans requiring the implantation of stem cells in the heart to grow collateral blood vessels based on a prophetic disclosure." Applicant again cites Kornowski, with the same argument on p. 22. This is not persuasive because the allegation that the allowed claims in the Kornowski '832 patent are based on a prophetic disclosure is not true. The '832 patent provides both in vitro and in vivo examples in support of the claimed subject matter. For instance, Example 4 provides functional and histological evidence of new blood

vessel formation after autologous bone marrow transplantation in an animal model of chronic myocardial ischemia. Thus, the examples that support the allowed claims are "prophetic" only in that the methods were not demonstrated in humans. First, the USPTO cannot, and does not, demand human clinical trials to demonstrate enablement for claims to methods of treating humans. Nothing in the rejections of record can logically be taken to imply such a demand. Nearly all patents in which biotechnological inventions are directed to the treatment of humans rely on animal, or even in vitro, evidence that the claimed methods are supported by a sound scientific basis, that the methods can work, and to provide enough guidance so that application to humans can proceed with a reasonable expectation of success. The sufficiency of the evidence is determined on a case-by-case basis. The instant specification provides no evidence comparable to that in the Kornowski '832 patent upon which to base a judgment.

37. Applicant's main point seems to be, "Apparently the Examiner fails to appreciate that the act of "writing down" a "prophetic" example, which describes an embodiment based upon predicted results rather than work actually conducted, is sufficient to satisfy a constructive reduction to practice" (Reply Brief, p. 12). Applicant's argument is not persuasive because it ignores the fact that proof of a constructive reduction to practice requires sufficient disclosure under the "how to use" and "how to make" requirements of 35 U.S.C. 112, first paragraph. Kawai v. Metlesics, 480 F.2d 880, 886, 178 USPQ 158, 163 (CCPA 1973). As was found in Ex parte Hitzeman, 9 USPQ2d 1821 (BPAI 1987), a single embodiment may provide broad enablement in cases involving predictable factors such as mechanical or electrical elements, but **more will be required in cases that involve unpredictable factors such as most chemical reactions and physiological activity**. See also In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA

1970); Amgen Inc. v. Chugai Pharmaceutical Co. Ltd., 927 F.2d 1200, 1212, 18 USPQ2d 1016, 1026 (Fed. Cir.), cert. denied, 502 U.S. 856 (1991). Conception and reduction to practice occur simultaneously in certain circumstances. Alpert v. Slatin, 305 F.2d 891, 894, 134 USPQ 296, 299 (CCPA 1962). "[I]n some **unpredictable areas of chemistry and biology**, there is no conception until the invention has been reduced to practice." MacMillan v. Moffett, 432 F.2d 1237, 1234-40, 167 USPQ 550, 552-553 (CCPA 1970). See also Hitzeman v. Rutter, 243 F.3d 1345, 58 USPQ2d 1161 (Fed. Cir. 2001) (conception simultaneous with reduction to practice where appellant lacked reasonable certainty that yeast's performance of certain intracellular processes would result in the claimed antigen particles); Dunn v. Ragin, 50 USPQ 472, 475 (Bd. Pat. Inter. 1941) (a new variety of asexually reproduced plant is conceived and reduced to practice when it is grown and recognized as a new variety). Under these circumstances, conception is not complete if subsequent experimentation reveals factual uncertainty which "so undermines the specificity of the inventor's idea that it is not yet a definite and permanent reflection of the complete invention as it will be used in practice." Burroughs Wellcome Co. v. Barr Labs., Inc., 40 F.3d 1223, 1229, 32 USPQ2d 1915, 1920 (Fed. Cir. 1994).

38. Even if interpreted in Applicant's most favored light, the most precise description of the cells to be administered in the instantly claimed methods is "bone marrow stem cells". Applicant did not distinguish between what is now being referred to as "global bone marrow stem cells" (a term used in the Reply Brief, footnote on p. 16, but not in the instant specification) and CD34+ mononuclear cells disclosed in Isner '887 (of record), for example. It was in fact Isner '887 who made the discovery that the CD34+ mononuclear cell population, present in both bone marrow and peripheral blood, comprises progenitors for endothelial cells as well as the previously identified hematopoietic progenitors. Kornowski '832 and Isner '887 seem to be in general agreement as they each disclose

cells derived from bone marrow as being able to stimulate neovascularization. The relationships among these cells remains uncertain, as is the precise population of cells that give rise to endothelial cells, as evidenced by Rabelink *et al*., Arthrosclerosis and Vascular Biology, 24:834-838, (2004) at p. 835. Therefore, the '887 and '832 patent disclosures and the Rabelink *et al*., reference represent subsequent experimentation that reveals factual uncertainty which "so undermines the specificity of the inventor's idea that it is not yet a definite and permanent reflection of the complete invention as it will be used in practice." See Burroughs Wellcome Co. v. Barr Labs., Inc., 40 F.3d 1223, 1229, 32 USPQ2d 1915, 1920 (Fed. Cir. 1994), cited above.

39. Even without post-filing references indicating uncertainty, Applicant's specification did not disclose with specificity which cells would or would not work for growing an artery. Applicant's assertion that "the claimed invention distinguishes from the Isner et al. patent by injecting global bone marrow stem cells which contain not only endothelial progenitor cells isolated and used by lsner but also hemapoietic progenitors, mesenchymal progenitors, and additional fractions requisite for growth of arteries' (footnote, p. 16) is not supported by the specification. It has already been established that the Examples most explicitly directed to artery formation (18, 19, and 36) do not mention any kind of cell. Examples 11 and 14-16, which at least mention cells, were discussed in the Examiner's Answer on pages 23-24. It is further noted herein that these examples teach in three places that "Living stem cells are harvested from the bone marrow, the blood of the patient, or from cell culture techniques (p.40, lines 27-28, p.41, lines 23-24, p. 42. lines 9-10). So even if these examples were directed to artery formation or heart muscle growth, they form no basis for distinguishing populations of marrow-derived cells as Applicant asserts. Examples 1-14 are apparently directed to formation of a tooth, Example 15 is directed to formation of a kidney, and Examples 16-17 are directed to formation of an eye. In examples 13 and 14, the artisan is

instructed to apply an electric spark to stem cells in order to activate MSX-1 and MSX-2 genes. In Examples 1-4, 10, and 11-17 the artisan is instructed to remove genes from skin tissue of a patient and then the artisan is given the nonsensical instruction to store the genes in nutrient culture medium. The genes are then to be added to culture medium along with stem cells, which apparently will result in growth of a tooth, kidney, or eye, depending on the genes used. These examples do not set forth a credible procedure to produce the asserted results and do not even mention growth of an artery.

40. Others sections of the specification that address cells include p. 37, lines, 19-23, which teach that, "Multifactorial and nonspecific cells (such as stem cells and germinal cells) can provide the necessary in vivo and in vitro cascade of genetic material once an implanted master control gene's transcription has been activated." Whatever this means, it certainly does not suggest the use of cells to grow an artery, nor does it provide any guidance as to how to use stem cells to grow an artery. In fact, the sentence states, "Likewise, any host cell, cloned cell, cultured cell, or cell would work", which, far from guiding the skilled artisan on how to perform a specific method, would have the skilled artisan believe that any cell can do anything.

41. Consider also the following sections from pages 47-48, which Applicant cites as guiding the use of bone marrow stem cells (Reply p. 24):

> Organs and/or tissues can be formed utilizing the patient's own cells. For example, a skin cell(s) is removed from the intraoral lining of a cheek. The cell is genetically screened to identify DNA damage or other structural and/or functional problems. Any existing prior art genetic screening technique can be utilized. Such methods can utilize lasers, DNA probes, PCR, or any other suitable device. If the cell is damaged, a healthy undamaged cell is, if possible, identified and selected. If a healthy cell can not be obtained, the damaged cell can be repaired by excision, alkylation, transition or any other desired method. A growth factor(s) is added to the cell to facilitate dedifferentiation and then redifferentiation and morphogenesis into an organ or function specific tissue. Any machine known in the art can be used to check the genetic fitness of the organ and its

> stage of morphogenesis. A cell nutrient culture may or may not be utilized depending on the desired functional outcome (i.e., growth of an artery, of pancreatic Islet cells, of a heart, etc.) or other circumstances. Replantation can occur at any appropriate stage of morphogenesis. The foregoing can be repeated without the patient's own cells if universal donor cells such a germinal cells are utilized. Germinal cells do not require a dedifferentiation. They simply differentiate into desired tissues or organs when properly stimulated. Similarly, the DNA utilized in the foregoing procedure can come from the patient or from any desired source.
>
> During reimplantation one of the patient's own cells is returned to the patient. During implantation, a cell not originally obtained from the patient is inserted on or in the patient.
>
> In the example above, if germinal cells (and in some cases, stem cells) are utilized a direct differentiation and morphogenesis into an organ can occur in vivo, ex vivo, or in vitro.

42. Thus, "the example above" exemplifies a skin cell(s) removed from the intraoral lining of a cheek. The artisan is instructed to screen for DNA damage, apparently any kind of damage to any gene, as no specific criteria are set forth to distinguish between "healthy" and "unhealthy". Likewise, the subsequent instruction to check genetic fitness is unclear—since this is supposed to be a new method, what constitutes "genetic fitness"? What genes are involved? And what machine does one use to determine it? The method then cites processes of DNA repair that can occur in intact cells, but does not teach how cause the cells to effect the desired repair. The method then suggests the addition of some unknown and undefined growth factors after which the cells can undergo processes of dedifferentiation and redifferentiation followed by morphogenesis into any desired organ or tissue. No such growth factor regimen is known in the art, and the specification does not teach one. It is not clear what "germinal cells" are but they are suggested to differentiate into desired tissues if properly stimulated. How to properly stimulate them to form an artery or any other organ is not disclosed. Consider also the instruction that, "A cell nutrient culture may or may not be utilized depending on the desired functional outcome."

The specification (p.41) contains the following definition: "The term "cell nutrient culture" as used herein can include any or any combination of the following: the extracellular matrix; conventional cell culture nutrients; and/or, a cell nutrient such as a vitamin. As such, the cell nutrient culture can be two- dimensional, three dimensional, or simply a nutrient, and is useful in promoting the processes of cellular dedifferentiation, redifferentiation, differentiation, growth, and development." By this definition, the phrase, "A cell nutrient culture may or may not be utilized" refers to the use of multiple agents that act upon cells. But the specification does not teach any factors or combination of factors that cause any cell to form an artery. "The example above", therefore, suggests that novel combinations of growth factors, ECM, nutrients, and vitamins will be able to cause cells to dedifferentiate, redifferentiate and form any organ or tissue, but does not teach what these combinations are.

43. So, even if "In the example above, if germinal cells (and in some cases, stem cells) are utilized a direct differentiation and morphogenesis into an organ" (specification p.48) is taken to mean that stem cells are to take the place of the skin cells or germinal cells of the example, so that use of stem cells to grow an artery is "contemplated", it does not even begin to teach one of skill in the art how to use stem cells to grow an artery. Note also that no mention is made of stem cells harvested from bone marrow. The cited section of the specification generally points toward some of the complex problems that might be encountered in regenerative medicine (choosing the right cell type, the possibility of preexisting genetic damage in the cells, the multiple factors that may direct pluripotent cells to differentiate in specified pathways) but does not teach the skilled artisan any solution to these problems. The specification suggests an idea that something can be done and then invites the skilled artisan to figure out how to do it.

44. To arrive at the methods of the instant claims, the skilled artisan is required select from these teachings to determine the cell to use to grow an artery or repair a heart. In some places it could be any cell. In others it is a skin cell that has undergone a mysterious process of dedifferentiation and redifferentiation. It might be a "germinal cell" "or in some cases stem cells". The cells are described as being "multifactorial and nonspecific", which does not provide any meaningful limitation as to the cells to use. Applicant has argued that one of skill would infer "stem cells" from sections of the specification that do not even mention any kind of cell. The very idea that bone marrow stem cells are to be used to grow an artery requires the skilled artisan to select this species out the infinitely large genus of factors applicant has defined. The notion that the specification aims to include "cells" in the genus of growth factors relies only on the fact that cells are, reasonably, "living organisms"; cells (and certainly not stem cells) are not explicitly included in the definition of growth factor (specification pages 20-21). The concept of using any kind of cell to grow an artery relies on selection of portions of the specification that contain the desired words, interpreting them in a manner that is contrary to the ordinary meanings of the key terms in the art, and putting them together, without specific prompting in the specification.

45. This is not merely a matter of written description, where the question is whether one of skill in the art can conceive the invention, this is also a matter of setting forth the invention in such full, clear, concise, and exact terms to enable a person of skill in the art to make and use the claimed methods. Thus, to say that "Applicant claims to have achieved something no one else had done, and then claims to have achieved it simply by writing it down" does not fully describe the how the instant specification fails to provide an enabling disclosure for the claimed methods. The writing that Applicant relies upon does not set forth the invention in such full, clear, concise, and exact terms to enable a person of skill in the art to make and use the claimed methods. The

skilled artisan is required to ignore hints of non-existent methods, unidentifiable cells, and nonsense such as "cascade of genetic material" and "The gene(s) is stored in an appropriate nutrient culture medium", and then look to the specification for guidance in a cutting-edge technology.

46. On pages 23-24 of the Reply Brief, Applicant alleges that the Fourth Supplemental Declaration of Dr. Heuser and the Third Supplemental Declaration of Dr. Lorincz had not been given due consideration. This is not persuasive. Case law has established that anticipation and operativeness are questions of fact; however, obviousness and enablement are questions of law. See In re Lindell, 155 USPQ 521; In re Chilowsky, 134 USPQ 515. The experts have given an opinion as to the ultimate legal conclusion of enablement, to which no weight is given. The underlying basis for the legal conclusion has been considered, as detailed in the Examiner's Answer on pages 38-42.

47. The Journal of Invasive Cardiology, Vol. 17, Jul 01 2005, Issue Number 7, published two discussions among medical experts, one regarding a presentation titled, "Progenitor Cell Transplantation and Function following Myocardial Infarction" (Author unknown)(http://www.invasivecardiology.com/article/4348), the other regarding a presentation by Holmes, "Tissue Engineering and Interventional Cardiology", (http://www.invasivecardiology.com/article/4347). These discussions include the following (emphasis added herein):

a. From "Progenitor Cell Transplantation and Function following Myocardial Infarction" (http://www.invasivecardiology.com/article/4348):

i. **O'Neill** "Do we know yet which would be the most efficient way — **if the appropriate cell were to be found** — to deliver the cells for the most efficient myogenesis?"

ii. **O'Neill**: The problem I have is that the stem cells are very sensitive to hypoxia; **they need an oxygenated environment in order to thrive**. Thus, if these cells are injected into a core infarct area, it will likely be hypoperfused and the ambient oxygen tension in that area may not be sufficient to support those cells… But my question is: Why would those cells stay at that target site? Also, **we are lacking basic scientific understanding** of the signals that allow the stem cells to hone in on that particular tissue.

iii. **Nikol**: "**These findings are not very convincing in my opinion, including the data from the Strauer group** which lacked a truly randomized control group. The problem with intramyocardial injections into infarcted areas is a real one, as you stated, in that there is no blood/oxygen supply and potentially arrhythmogenic foci are created… Also, **there may not be a homogeneous distribution of cells**…**"**

iv. **Gonschior** , "It would be very smart to just inject the cells intravenously… **In fact, it turned out that endocardial delivery of these cells was the most efficient**"

v. **O'Neill**: "…bone marrow is unfiltered…Basically, the injection contains the "kitchen sink" **and we hope that the right cells go to the right place and do the right thing**.

b. From "Tissue Engineering and Interventional Cardiology", (http://www.invasivecardiology.com/article/4347):

vi. **Holmes**: "**We are already in the middle of human trials before obtaining adequate scientific data about which specific cells to use, how many cells, when to deliver them, and how to deliver them**…when these different sorts of cells are delivered intravenously, they go to the lungs and have a "tremendous time," and they don't reach the myocardium. So while it makes perfect sense to use the intravenous approach, these cells are filtered out in the lungs and remain there. If those cells are active and produce cytokines, perhaps that's all we would want to use them for. Maybe these cells aren't the magic solution, and maybe we don't have a clue about this. Perhaps we can use these cells for the cytokines they produce systemically and they will cause other bone marrow cells to hone in on the site of injury. **But at the present, we just don't know enough about this process**.

vii. **Whitlow**: "…if you are adding islands of tissue in the left ventricle that is already damaged, these islands of tissue are not enervated in the same way as the surrounding tissue and the conduction properties aren't the same. You would theorize that this could set up re-entry circuits. Thus, **ventricular arrhythmia presents an enormous problem** in terms of conducting studies because many of these patients are going to die from their underlying disease… We know from the animal studies that efficacy increases with higher doses of cell therapy, but **we**

have yet to find what a potentially toxic dose is for the size of the island of cells that produce arrhythmias."

48. It is clear that questions of choice of cell, dosing, timing, means of delivery, and cell survival, were still unanswered in these discussions that took place about seven years after the instant specification was filed. These concerns are the same as those raised herein and in the rejections of record with respect to the lack of guidance provided by the instant specification. Clearly, considerable experimentation had taken place; complications, such as arrhythmia due to uneven distribution cells, had been identified. There was a general agreement that more experimentation was needed. Thus, all arguments that post-filing successes reported by others were predictable and did not require much experimentation are thoroughly refuted. It is further noted that one of the participants in these discussions was Dr. Richard Heuser, a Declarant of record in the instant case. If Applicant's arguments are to be accepted, then Dr. Heuser, having "read and understood" the instant specification, was in possession of answers to the controversies under discussion. One wonders why Dr. Heuser did not speak up and enlighten his colleagues.

49. In response to the finding that the instant specification does not provide guidance as to how an old material, such as bone marrow stem cells, and methods, such as injection into heart muscle, can be used to achieve growth of a new tissue, such as an artery, Applicant has replied, "The answer is simple. The skilled medical doctor's manipulation ends with the implantation or reimplantation of the bone marrow stem cells in the heart of the patient in sufficient dosages to affect repair of the dead or damaged portion of the patient's heart (Reply, p. 21)." It is clear from the discussion above, that many of the critical decisions, manipulation, and preparations take place before the injection is made. Clearly, simply knowing how to inject cells is not enough to

perform a method of repairing a damaged portion, replacing a dead portion, or growing a new portion of an existing heart. It has been stated repeatedly in the record that the courts have stated that patent protection is granted in return for an enabling disclosure, not for vague intimations of general ideas that may or may not be workable. Tossing out the mere germ of an idea does not constitute an enabling disclosure. Reasonable detail must be provided in order to enable members of the public to understand and carry out the invention. See *Genentech v. Novo Nordisk A/S* (CAFC) 42 USPQ2d 1001 (1997). While evidence of a fully developed clinical procedure is not required for a patent, the notion that the new result, cardiac muscle and artery growth, can be achieved using old materials (bone marrow stem cells) and old methods (injection) (see Reply p.24), was indeed "a germ of an idea" at the time the instant application was filed. The instant specification does not even clearly enunciate this germ of an idea, let alone provide an enabling disclosure of how to make and use the claimed invention. The post-filing references of record are not "confirmation of the claimed results" as Applicant asserts (Reply, p. 21) but rather they are evidence of further experimentation involved in the act of invention.

50. The rejection of record has given careful consideration to the nature of the invention, the state of the prior art, the predictability or lack thereof in the art, the level of skill in the art, the amount of direction or guidance present, the presence or absence of working examples, the breadth of the claims, and the quantity of experimentation needed. It has been acknowledged that the level of skill in the art is high. However, the remaining factors indicate that the each of the claims under consideration must be rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement.

Conclusion

51. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Daniel C. Gamett, PhD., whose telephone number is (571)272-1853. The examiner can normally be reached on 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Manjunath N. Rao can be reached on 571 272 0939. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

DCG
Art Unit 1647

/David S Romeo/
Primary Examiner, Art Unit 1647